BACKGROUNDER
NATIONAL CENTER FOR COMPLEMENTARY AND ALTERNATIVE MEDICINE

Questions and Answers: NIH Glucosamine/chondroitin Arthritis Intervention Trial (GAIT)

About the Study

What is the Glucosamine/chondroitin Arthritis Intervention Trial (GAIT)?
GAIT is the first, large-scale, multicenter clinical trial in the United States to test the effects of the dietary supplements glucosamine hydrochloride (glucosamine) and sodium chondroitin sulfate (chondroitin sulfate) for treatment of knee osteoarthritis. The study tested whether glucosamine and chondroitin sulfate used separately or in combination reduced pain in participants with knee osteoarthritis.

The University of Utah, School of Medicine coordinated this study, which was conducted at 16 rheumatology research centers across the United States. The National Center for Complementary and Alternative Medicine (NCCAM) and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), two components of the National Institutes of Health (NIH), funded GAIT.

What was the purpose of the study?
Previous studies in the medical literature had conflicting results on the effectiveness of glucosamine and chondroitin sulfate as treatments for osteoarthritis. GAIT was designed to test the short-term (6 months) effectiveness of glucosamine and chondroitin sulfate in reducing pain in a large number of participants with knee osteoarthritis.

What was the basic design of the study?
In GAIT, participants were randomly assigned to one of five treatment groups: (1) glucosamine alone, (2) chondroitin sulfate alone, (3) glucosamine and chondroitin sulfate in combination, (4) celecoxib, or (5) a placebo (an inactive substance that looks like the study substance). Glucosamine and chondroitin sulfate and their combination were compared to a placebo to evaluate whether these substances significantly improve joint pain. Celecoxib, which is a prescription drug effective in managing osteoarthritis pain, was also compared to placebo to validate the study design.

To reduce the chance of biased results, the study was double-blinded—neither the researchers nor the participants knew which of the five treatment groups the participants were in. Participants received treatment for 24 weeks. Participants were evaluated at the start of the study and at weeks 4, 8, 16, and 24 and closely monitored for improvement of their symptoms as well as for any possible adverse reactions to the study agents. X-rays documented each participant's diagnosis of osteoarthritis. Participants were also stratified into two pain subgroups—mild pain 1,229 participants (78 percent) and moderate-to-severe pain 354 participants (22 percent).

The primary outcome of the study was defined as at least a 20 percent reduction in pain at 24 weeks. All participants had the option to use up to 4000 mg of acetaminophen, as needed, to control pain from osteoarthritis throughout the study, except for the 24 hours prior to having their knee assessed. Acetaminophen use was low: on average, participants used fewer than two 500 mg tablets per day.

What did GAIT cost?
The primary GAIT study cost just over $12.5 million.

Study Background

What is osteoarthritis?
More than 20 million adults in the United States live with osteoarthritis—the most common type of arthritis. Osteoarthritis, also called degenerative joint disease, is caused by the breakdown of cartilage, which is the connective tissue that cushions the ends of bones within the joint. Osteoarthritis is characterized by pain, joint damage, and limited motion. The disease generally occurs late in life, and most commonly affects the hands and large weight-bearing joints, such as the knees. Age, female gender, and obesity are risk factors for this condition.

What are glucosamine and chondroitin sulfate?
Glucosamine and chondroitin sulfate are natural substances found in and around the cells of cartilage. Glucosamine is an amino sugar that the body produces and distributes in cartilage and other connective tissue, and chondroitin sulfate is a complex carbohydrate that helps cartilage retain water. In the United States, glucosamine and chondroitin sulfate are sold as dietary supplements, which are regulated as foods rather than drugs.

What is celecoxib?
Celecoxib (brand name Celebrex) is a type of nonsteroidal anti-inflammatory drug (NSAID), called a COX-2 inhibitor. Like traditional NSAIDs, celecoxib blocks the COX-2 enzyme in the body that stimulates inflammation. Unlike traditional NSAIDs, however, celecoxib does not block the action of COX-1 enzyme, which is known to protect the stomach lining. As a result, celecoxib reduces joint pain and inflammation with reduced risk of gastrointestinal ulceration and bleeding. Recent reports have linked possible cardiovascular side effects to COX-2 inhibitors. Although GAIT was not designed to study the safety of celecoxib, participants were monitored for adverse events and no increase in such side effects was observed.

What doses were used for the various treatments?
The doses used in GAIT were based on the doses seen in the prevailing scientific literature.

- Glucosamine alone: 1500 mg daily given as 500 mg three times a day
- Chondroitin sulfate alone: 1200 mg daily given as 400 mg three times a day
- Glucosamine plus chondroitin sulfate combined: same doses—1500 mg and 1200 mg daily
- Celecoxib: 200 mg daily
- Acetaminophen: participants were allowed to take up to 4000 mg (500 mg tablets) per day to control pain, except for the 24 hours before pain was assessed.

Who provided the source materials for making the glucosamine and chondroitin sulfate products used in GAIT?
- Glucosamine was donated in part by Ferro Pfanstiehl Laboratories, Inc., Waukegan, IL, through Wilke Resources.
- Chondroitin sulfate was donated by Bioiberica, S.A., Barcelona, Spain.

The study agents were manufactured by Albuquerque Veterans Affairs (VA) Cooperative Studies Program Clinical Research Pharmacy.

Where did the other study products come from?
- Acetaminophen was donated by McNeil Consumer and Specialty Pharmaceuticals, Fort Washington, PA.
- Celecoxib was purchased from Pfizer.

Where was the study conducted?
The University of Utah, School of Medicine, Salt Lake City, UT, served as the coordinating study center and oversaw the research and recruitment efforts of the 16 study centers. The study was led by Daniel O. Clegg, M.D., a Professor of Medicine and Chief of Rheumatology, Division of Rheumatology, University of Utah, School of Medicine. The GAIT biostatistician was Domenic J. Reda, Ph.D., from the Hines VA Cooperative Studies Program, which served as the study data management and analysis center. The GAIT Clinical Research Pharmacist was Crystal L. Harris, Pharm.D., at the Albuquerque VA Cooperative Studies Program Clinical Research Pharmacy, which manufactured, packaged, distributed, and provided analytical testing of the study agents along with regulatory support for GAIT. The 16 study centers and their lead investigators were:

- University of Alabama at Birmingham, Birmingham, AL; Larry W. Moreland, M.D.
- University of Arizona, Tucson, AZ; David Yocum, M.D.
- Cedars-Sinai Medical Center, Los Angeles, CA; Michael Weisman, M.D.
- University of California Los Angeles, Los Angeles, CA; Daniel Furst, M.D.
- University of California San Francisco, San Francisco, CA; Nancy Lane, M.D.
- Northwestern University, Chicago, IL; Thomas J. Schnitzer, M.D.
- Indiana University, Indianapolis, IN; John Bradley, M.D.
- The Arthritis Research and Clinical Centers, Wichita, KS; Frederick Wolfe, M.D.
- University of Nebraska Medical Center, Omaha, NE; James O'Dell, M.D.

- Hospital for Joint Diseases, New York, NY; Clifton Bingham, III, M.D.
- Case Western Reserve University, Cleveland, OH; Michele Hooper, M.D.
- University of Pennsylvania, Philadelphia, PA; H. Ralph Schumacher, Jr., M.D.
- University of Pittsburgh, Pittsburgh, PA; Chester Oddis, M.D.
- Presbyterian Hospital of Dallas, Dallas, TX; John J. Cush, M.D.
- University of Utah, Salt Lake City, UT; Christopher G. Jackson, M.D.
- Virginia Mason Medical Center, Seattle, WA; Jerry Molitor, M.D.

Key Results

What were the key results of the study?
Researchers found that:

- Participants taking the positive control, celecoxib, experienced statistically significant pain relief versus placebo—about 70 percent of those taking celecoxib had a 20 percent or greater reduction in pain versus about 60 percent for placebo.

- Overall, there were no significant differences between the other treatments tested and placebo.

- For a subset of participants with moderate-to-severe pain, glucosamine combined with chondroitin sulfate provided statistically significant pain relief compared to placebo—about 79 percent had a 20 percent or greater reduction in pain versus about 54 percent for placebo. According to the researchers, because of the small size of this subgroup these findings should be considered preliminary and need to be confirmed in further studies.

- For participants in the mild pain subset, glucosamine and chondroitin sulfate together or alone did not provide statistically significant pain relief.

How many people participated in the study and who were they?
A total of 1,583 people participated in the study. People age 40 or older with knee pain and documented x-ray evidence of osteoarthritis were eligible to participate. Participants could not have used glucosamine for 3 months and chondroitin sulfate for 6 months prior to entering the study. Participants were about 59 years of age, on average, and nearly two-thirds of participants were women. Of the 1,583 study participants, 78 percent (1,229) were in the mild pain subgroup and 22 percent (354) were in the moderate-to-severe pain subgroup.

Were there any side effects from the treatments?
There were 77 reports of serious adverse effects during the study. Of those 77, only 3 were attributed to study treatments. Most side effects were mild, such as upset stomach, and were spread evenly across the different treatment groups. In addition, although GAIT was not designed to evaluate these risks, no change in glucose tolerance was seen for glucosamine nor was an increased incidence of cardiovascular events seen with celecoxib.

Consumer Information and Next Steps

Should people with osteoarthritis use glucosamine and chondroitin sulfate?
People with osteoarthritis should work with their health care provider to develop a comprehensive plan for managing their arthritis pain: eat right, exercise, lose excess weight, and use proven pain medications. If people have moderate-to-severe pain, they should talk with their health care provider about whether glucosamine plus chondroitin sulfate is an appropriate treatment option.

Can U.S. consumers get the glucosamine and chondroitin sulfate products used in GAIT?
Identical products may not be commercially available. GAIT was conducted under an Investigational New Drug application filed with the U.S. Food and Drug Administration (FDA). All of the products used in the study were developed for the study and subject to the FDA's pharmaceutical regulations. The products were evaluated and manufactured by the VA Cooperative Studies Program Clinical Research Pharmacy, an FDA-licensed clinical research pharmacy center. The glucosamine and chondroitin sulfate used were tested for purity, potency, quality, and consistency among batches. Products were retested for stability throughout the study.

Will the GAIT team continue to do research on glucosamine and chondroitin sulfate?
GAIT includes an ancillary study, which is still ongoing, that will assess whether glucosamine and chondroitin sulfate can reduce or halt the progression of knee osteoarthritis following additional treatment. About one-half of the participants enrolled in GAIT will be treated for an additional 18 months. As in the primary study, participants will not know to which treatment group they belong. Researchers will compare x-rays taken at the beginning of the study and after 1 and 2 years of treatment to identify changes in the knee joints as a result of treatment. Results are expected in about a year.

For More Information

NCCAM Clearinghouse

The NCCAM Clearinghouse provides information on CAM and NCCAM, including publications and searches of Federal databases of scientific and medical literature. The Clearinghouse does not provide medical advice, treatment recommendations, or referrals to practitioners.

Toll-free in the U.S.: 1-888-644-6226
International: 301-519-3153
TTY (for deaf and hard-of-hearing callers): 1-866-464-3615
Web site: nccam.nih.gov
E-mail: info@nccam.nih.gov

National Institute of Arthritis and Musculoskeletal and Skin Diseases

For information on rheumatic diseases such as osteoarthritis and diseases of the musculoskeletal and skin systems, contact the NIAMS Information Clearinghouse.

Toll-free in the U.S.: 1-877-22-NIAMS
Telephone: 301-495-4484
Web site: www.niams.nih.gov/hi/index.htm
Address: NIAMS/National Institutes of Health, 1 AMS Circle, Bethesda, MD 20892-3675

NIH Office of Dietary Supplements

For scientific citations and abstracts on dietary supplements, visit the ODS Web site for access to the International Bibliographic Information on Dietary Supplements database.

Web site: ods.od.nih.gov

U.S. Food and Drug Administration

For information on dietary supplement labeling requirements and safety monitoring, order the FDA Guide to Dietary Supplements from the U.S. Food and Drug Administration, Center for Food Safety and Applied Nutrition.

Toll-free in the U.S.: 1-800-FDA-4010
Web site: www.cfsan.fda.gov

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